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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/603,320 | 06/26/00 | BURZYNSKI S | BURG:046/KAM |

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| EXAMINER | |
|---|---|
| BAHAR, M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | 8 |

**DATE MAILED:** 08/14/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/603,320 | BURZYNSKI, STANISLAW R. | |
| | Examiner | Art Unit | |
| | Mojdeh Bahar | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,8,16 and 19-23* is/are pending in the application.

4a) Of the above claim(s) *16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicant's amendment and response to the first office action of January 30, 2001, submitted April 30, 2001 (Paper No.7) is acknowledged.

Claims 1, 4, 8 and 19-23 are herein examined on the merits in so far as they read on the elected specie.

This application contains claim 16 drawn to an invention nonelected with traverse in Paper No. 4. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 8 and19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over applicant's admissions regarding the prior art at pages 2-3 of the specification in view of Hendry et al (USPN 5,238,947), all of record in the previous office action.

Applicant discloses that compounds such as 3-phenylacetylamino-2,6-piperidinedione and its hydrolysis products are known to block a reaction in the pathway of cholesterol biosynthesis, and as a result these compounds may lower serum cholesterol level. See page 3, lines 18-18 in the specification particularly.

Applicant's admissions regarding the prior art do not expressly disclose any relationship between the sodium salt of phenylacetylglutamine and 3-phenylacetylamino-2,6,piperidinedione. Moreover, applicant's admission do not expressly teach the therapeutic amounts employed herein, nor do they teach compositions containing the elected compound, phenylacetylglutamine sodium.

Hendry et al. discloses that the initial hydrolysis product of 3-phenylacetylamino-2,6-piperidinedione is phenylacetylglutamine, which is produced in vivo from phenylacetic acid and glutamine. In fact, Hendry et al. teaches that 3-phenylacetylamino-2,6-piperidinedione may be cyclized from phenylacetylglutamine in vivo,(Col. 2 lines 40-44).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ phenylacetylglutamine (or any salt thereof) in lieu of 3-phenylacetylamino-2,6-piperidinedione as cholesterol lowering agents in methods to inhibit or treat hypercholesterolemia in an affected patient.

One of ordinary skill in the art would have been motivated to combine these teachings in order to employ phenylacetylglutamine sodium in a method of treating or inhibiting hypercholesterolemia because phenylacetylamino-2,6-piperidinedione is known to be hydrolyzed in a host in vivo to produce phenylacetylglutamine. Therefore, similar antihypercholesterolemic effects in the host (i.e. affected patient) for both compounds would be reasonably expected. Given the current state of the art, determining the active ingredient dosage level is well within the Skilled Artisan's purview and the benefits of achieving such maximization obvious, to said Skilled Artisan. The optimization of amounts of active ingredients to be employed is considered within the skill of the artisan.

Further, the incorporation of known active agents in compositions with pharmaceutical carrier materials is conventional in the art.

Applicant's remarks (Paper No. 7) submitted April 30, 2001 regarding the non-obviousness of the claimed invention have been considered but are not persuasive as discussed herein below.

Applicant argues that applicant's admissions regarding the prior art at page 3, lines 18-23 of the specification (used in the prior office action) that 3-phenylacetylamino-2,6-piperidinedione and its derivatives can block a specific step in the cholesterol biosynthetic pathway is to be interpreted to mean that these compounds have been shown to block this enzymatic activity *in vitro*, and not *in vivo*. Applicant further argues that the *in vivo* cholesterol reduction capabilities of the compound were known to the inventor only. These remarks and applicant's incorporation of the expression "affected patient" in the amended base claim 1 have been considered but are not persuasive as to non-obviousness of the claimed invention.

In the section entitled **"Background of the invention"** of the specification at page 3, lines 18-23, applicant admits:

"It has been known for some time that compounds such as 3-phenylacetylamino-2,6-piperidinedione and its hydrolysis products such as phenylacetic acid, and salts, precursors, and analogs thereof (together "3-phenylacetylamino-2,6-piperidinedione and its derivatives"), can block the formation of iso-pentenylpyrophosphate from 5-pyrophosphomevalonate, a reaction in the pathway of cholesterol biosynthesis; as a result these compounds may lower serum cholesterol levels."

Applicant's admissions do not address the presence or absence of a host, neither is there any mention of *in vitro* vs. *in vivo* application or employment of these compounds. Therefore, applicant's remarks regarding mere *in vitro* enzyme activity blockage in the prior art as represented by his admissions in the specification are unpersuasive. Furthermore, even if, applicant's admissions in the specification regarding the prior art were limited to *in vitro* enzyme activity, it is well known in the pharmaceutical art that the purpose of *in vitro* experimentation with pharmaceutical actives is to ultimately administer the active composition *in vivo* to an affected host/patient for some sort of therapy. This sort of in vitro testing is conventional in the pharmaceutical art. In fact, applicant himself is cited in Hendry et al. to have used in vitro experimentation to predict therapeutic efficacy for later in vivo administration of the same pharmaceutical composition, see particularly col. 2, lines 16-48. Therefore one of ordinary skill in the art would have reasonably believed that 3-phenylacetylamino-2,6-piperidinedione and its derivatives known to block a specific step in the cholesterol biosynthetic pathway and in turn block cholesterol synthesis result in the lowering of blood cholesterol levels in vitro or in vivo broadly, as indicated by applicant's admissions regarding the prior art, or even merely in vitro as argued by applicant in Paper No. 7 would also block the same pathway and reduce blood cholesterol *in vivo* in a patient as well, absent evidence to the contrary.

Applicant further argues that there is no motivation to combine applicant's admissions regarding the prior art (of record in Paper No. 6) with the teaching of Hendry et al. Applicant's arguments in this regard have been considered but are not found persuasive. Applicant has admitted at page 2-3 of the specification that 3-phenylacetylamino-2,6-piperidinedione and its derivatives are known to block a specific step in the cholesterol biosynthetic pathway, broadly.

Hendry et al. teaches that the initial hydrolysis product of 3-phenylacetylamino-2,6-piperidinedione is phenylacetylglutamine, which is produced *in vivo* from phenylacetic acid and glutamine. Therefore, one of ordinary skill in the art would have been motivated to combine the prior art teachings in Hendry et al. that phenylacetylglutamine is a known *in vivo* hydrolysis product of 3-phenylacetylamino-2,6-piperidinedione and its derivatives with the prior art teachings discussed by applicant in the specification relating to the known activity of 3-phenylacetylamino-2,6-piperidinedione and its derivatives and hydrolysis products to block a specific step in the cholesterol biosynthetic pathway and in turn block cholesterol synthesis *in vitro* or *in vivo* broadly, and result in the lowering of blood cholesterol levels (or even merely *in vitro* as argued by applicant in Paper No. 7) because known *in vivo* hydrolysis products of 3-phenylacetylamino-2,6-piperidinedione and its derivatives, including phenylacetylglutamine, would have been reasonably expected to block the same biosynthetic pathway as 3-phenylacetylamino-2,6-piperidinedione and its derivatives and reduce blood cholesterol in a manner similar to these compounds, *in vivo* in a patient as well, absent evidence to the contrary.

The claimed methods of treating or inhibiting hypercholesterolemia or hypertriglyceridemia in an affected patient are considered obvious over the cited prior art, absent evidence to the contrary. No such evidence is seen.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mojdeh Bahar whose telephone number is (703) 305-1007. The examiner can normally be reached on Monday, Tuesday, Thursday, and Friday from 8:30 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Mojdeh Bahar
Patent Examiner
July 30, 2001

MINNA MOEZIE, J.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600